Example of a biochemical cascade: Mitogen Activated Protein Kinase (MAPK) in Solution

MAPK CASCADE

MAPK gives a canonical example of a phosphorylation cascade, a sequence of phosphorylation reactions where the active, or phosphorylated form (sometimes doubly-phosphorylated form), of a protein at the kth step of the cascade subsequently catalyzes phosphorylation of the protein on the k+1st step of the cascade.

NOTATION USED FOR REACTIONS

We might represent a catalytic (e.g., enzymatic) reaction in (at least) the following four different ways:

1. $V \Rightarrow W$, read as "V activates W," e.g., V catalyzes the formation of an object called W (V may be an enzyme and W its product). It is not clear in this notation what W is formed from (the source) or what rate constants (and other data) describe this process.
2. $U \overset{V}{\Rightarrow} W$, read as "$V$ facilitates the conversion of U to W," e.g., when V is an enzyme with substrate U and product W. Rate constants and other potential reactants (such as Ca or ATP) are still hidden, and it is not clear whether U is converted into W or if U still remains, perhaps in an altered form, after the reaction occurs.
3. As a biochemical reaction such as
$$U + V \underset{d}{\overset{a}{\rightleftharpoons}} U \cdot V \overset{k}{\rightarrow} W + V$$
where $U \cdot V$ is the molecular complex formed by combining U and V, and a, d and k are rate constants. In this reaction U is converted into (and is assumed to replace) W. Other reactants are still suppressed.In an alternative scheme, U is replaced by two products, U' and W,
$$U + V \underset{d}{\overset{a}{\rightleftharpoons}} U \cdot V \overset{k}{\rightarrow} U' + W + V$$
We will focus on the first scheme only.
4. As a set of basic chemical reactions such as
$$U + V \overset{a}{\rightarrow} U \cdot V,\ U \cdot V \overset{d}{\rightarrow} U + V,\ U \cdot V \overset{k}{\rightarrow} W + V$$
Here U is literally converted into W by V. In the case of phosphorylation we might actually want to replace the third reaction with
$$U \cdot V + ATP \overset{k}{\rightarrow} U^* + V + ADP$$
where U^* the phosphorylated version of U. In general we will assume that there is ample ATP available for phosphorylation to occur, and we will instead write the set of reactions as
$$U + V \overset{a}{\rightarrow} U \cdot V,\ U \cdot V \overset{d}{\rightarrow} U + V,\ U \cdot V \overset{k}{\rightarrow} U^* + V$$
with similar notation for the removal of phosphate groups. The following examples apply specifically to a **phosphorylation** cascade.

SIMPLE CASCADE NOTATION:

A cascade would be written as

$$X \Rightarrow A \Rightarrow B \Rightarrow C$$

which we would read as "*X activates A, A activates B, B activates C.*" An example would be

$$RAFK \Rightarrow RAF \Rightarrow MEK \Rightarrow MAPK.$$

MORE DETAILED CASCADE NOTATION

In this notation we explicitly show the "input," "output," and "catalyst" of each state. A three-stage MAP kinase cascade would be written as

$$A \overset{X}{\Rightarrow} A^* \qquad \text{(first stage)}$$
$$B \overset{A^*}{\Rightarrow} B^* \overset{A^*}{\Rightarrow} B^{**} \qquad \text{(second stage)}$$
$$C \overset{B^{**}}{\Rightarrow} C^* \overset{B^{**}}{\Rightarrow} C^{**} \qquad \text{(third stage)}$$

We read this as: "*X phosphorylates A, the phosphorylated form A (called A*) phosphorylates B twice, and the doubly phosphorylated form of B phosphorylates C twice.*" The input to the cascade is X and the output is C^{**}. More common names for A, B and C are MAPKKK, MAPKK, and MAPK, respectively. A typical example would be RAF (MAPKKK), MEK (MAPKK) and MAPK, with the input signal being RAFK (RAF kinase).

BIOCHEMICAL REACTIONS

Actual Phosphorylation Reactions:

$$A + X \underset{d_1}{\overset{a_1}{\rightleftharpoons}} A \cdot X \overset{k_1}{\rightarrow} A^* + X$$

$$B + A^* \underset{d_3}{\overset{a_3}{\rightleftharpoons}} B \cdot A^* \overset{k_3}{\rightarrow} B^* + A^*$$

$$B^* + A^* \underset{d_5}{\overset{a_5}{\rightleftharpoons}} B^* \cdot A^* \overset{k_5}{\rightarrow} B^{**} + A^*$$

$$C + B^{**} \underset{d_7}{\overset{a_7}{\rightleftharpoons}} C \cdot B^{**} \overset{k_7}{\rightarrow} C^* + B^{**}$$

$$C^* + B^{**} \underset{d_9}{\overset{a_9}{\rightleftharpoons}} C^* \cdot B^{**} \overset{k_9}{\rightarrow} C^{**} + B^{**}$$

Reverse Enzyme (phosphatase) Reactions:

$$A^* + AP \underset{d_2}{\overset{a_2}{\rightleftharpoons}} A^* \cdot AP \overset{k_2}{\rightarrow} A + AP$$

$$B^* + BP \underset{d_4}{\overset{a_4}{\rightleftharpoons}} B^* \cdot BP \overset{k_4}{\rightarrow} B + BP$$

$$B^{**} + BP \underset{d_6}{\overset{a_6}{\rightleftharpoons}} B^{**} \cdot BP \overset{k_6}{\rightarrow} B^* + BP$$

$$C^* + CP \underset{d_8}{\overset{a_8}{\rightleftharpoons}} C^* \cdot CP \overset{k_8}{\rightarrow} C + CP$$

$$C^{**} + CP \underset{d_{10}}{\overset{a_{10}}{\rightleftharpoons}} C^{**} \cdot CP \overset{k_{10}}{\rightarrow} C^* + CP$$

Jet Propulsion Laboratory, California Institute of Technology

DIFFERENTIAL EQUATIONS:

Protein concentrations: Input Signal Protein

$$[X]' = -a_1[A][X] + (d_1 + k_1)[A \cdot X]$$

Protein concentrations: First Stage of Cascade

$$[A]' = -a_1[A][X] \; + d_1[A \cdot X] + k_2[A * \cdot AP]$$

$$[A*]' = -a_2[AP][A*] - a_3[A*][B] - a_5[A*][B*] + d_2[A * \cdot AP] + (d_3 + k_3)[B \cdot A*] + (d_5 + k_5)[B * \cdot A*] + k_1[A \cdot X]$$

Protein concentrations: Second Stage of Cascade

$$[B]' = -a_3[A*][B] + d_3[B \cdot A*] + k_4[B * \cdot BP]$$

$$[B*]' = -a_4[BP][B*] - (a_5 - \mathrm{d}_5)[A*][B*] + d_4[B * \cdot BP] + k_3[B \cdot A*] + k_6[B * * \cdot BP]$$

$$[B * *]' = -a_6[BP][B * *] - a_7[B * *][C] - a_9[B * *][C*] + d_6[B * * \cdot BP] + (d_7 + k_7)[C \cdot B * *] + (d_9 + k_9)[C * \cdot B * *] + k_5[B * \cdot A*]$$

Protein concentrations: Third Stage of Cascade

$$[C]' = -a_7[B * *][C] + d_7[C \cdot B * *] + k_8[C * \cdot CP]$$

$$[C*]' = -a_8[CP][C*] - a_9[B * *][C*] + d_8[C * \cdot CP] + d_9[C * \cdot B * *] + k_{10}[C * * \cdot CP] + k_7[C \cdot B * *]$$

$$[C * *]' = -a_{10}[CP][C * *] + d_{10}[C * * \cdot CP] + k_9[C * \cdot B * *]$$

Intermediate Complex Concentrations:

$$[A \cdot X]' = a_1[A][X] - (d_1 + k_1)[A \cdot X]$$

$$[B * \cdot A*]' = a_5[A*][B*] - (d_5 + k_5)[B * \cdot A*]$$

$$[B \cdot A*]' = a_5[A*][B] - (d_3 + k_3)[B \cdot A*]$$

$$[C * \cdot B * *]' = a_9[B * *][C*] - (d_9 + k_9)[C * \cdot B * *]$$

$$[C \cdot B * *]' = a_7[B * *][C] - (d_7 + k_7)[C \cdot B * *]$$

Phosphatase Concentrations:

$$[AP]' = -a_2[AP][A*] + (d_2 + \mathrm{k}_2)[A * \cdot AP]$$

$$[BP]' = -a_4[BP][B*] - a_6[BP][B * *] + (d_4 + \mathrm{k}_4)[B * \cdot BP] + (d_6 + \mathrm{k}_6)[B * * \cdot BP]$$

$$[CP]' = -a_{10}[CP][C * *] - a_8[CP][C*] + (d_8 + k_8)[C * \cdot CP] + (d_{10} + k_{10})[C * * \cdot CP]$$

Intermediate Concentrations (with Phosphatase in complex)

$$[A * \cdot AP]' = a_2[AP][A*] - (d_2 + k_2)[A * \cdot AP]$$

$$[B * \cdot BP]' = a_4[BP][B*] - (d_4 + k_4)[B * \cdot BP]$$

$$[B * * \cdot BP]' = a_6[BP][B * *] - (d_6 + k_6)[B * * \cdot BP]$$

$$[C * \cdot CP]' = a_8[CP][C*] - (d_8 + k_8)[C * \cdot CP]$$

$$[C * * \cdot CP]' = a_{10}[CP][C * *] - (d_{10} + k_{10})[C * * \cdot CP]$$

No guarantee is made of the accuracy of the equations in this document.